Amendments to the Claims:

Please cancel claims 18, 20 to 27 and 60 to 65 without prejudice or disclaimer.

Please add new claims 67 to 86 as follows:

This listing of claims will replace all prior versions and listing of claims in the application.

Listing of Claims:

Claims 1 to 66. (cancelled)

67. (new) A method of treating hypertension in a mammal in need of said treatment comprising administering an effective amount of a peptide comprising at least nine contiguous amino acids residues selected from an amino acid sequence of a transmembrane domain of an alpha-1A adrenergic receptor.

68. (new) A method of treating hypertension in a mammal in need of said treatment comprising administering an effective amount of a peptide comprising at least nine contiguous amino acids selected from an amino acid sequence of a transmembrane domain of a alpha-1A adrenergic receptor, residues wherein the peptide contains one or more conservative amino acid substitutions in the nine contiguous amino acids.

69. (new) The method according to claim 67 or 68 wherein the peptide binds to a transmembrane domain of the alpha-1A adrenergic receptor.

70. (new) The method according to claim 69 wherein the peptide inhibits the activity of the alpha-1A adrenergic receptor.

71. (new) The method according to claim 70 wherein the inhibition of the activity of the alpha-1A adrenergic receptor induces vasodilation or inhibits vasoconstriction.

72. (new) The method according to claim 67 or 68 wherein the peptide retains a helical confirmation.

73. (new) The method according to claim 67 or 68 wherein the peptide comprises up to twenty-six amino acid residues.

74. (new) The method according to claim 67 or 68 wherein one or more of the amino acid residues of the peptide contains a side chain modification.

75. (new) The method according to claim 67 or 68 wherein one or more of the amino acid residues of the peptide is a non-natural amino acid.

76. (new) The method of claim 67 or 68 wherein the peptide is altered to increase plasma half-life following administration.

77. (new) The method of claim 76 wherein the peptide is conjugated to one or more water-soluble polymers.

78. (new) The method of claim 76 wherein the peptide is incorporated into a polymeric matrix.

79. (new) The method according to claim 67 or 68 wherein the amino acid sequence of the transmembrane domain of the alpha-1A adrenergic receptor is selected from the group consisting of:

GVGVGVFLAAFILMAVAGNLLVILSV (SEQ ID NO: 23);
FIVNLAVADLLLSATVLPFSATMEVL (SEQ ID NO:24);
DVWAAVDVLCCTASILSLCTISV (SEQ ID NO: 25);
AAILALLWVVALVVSVGPLLGWKEP (SEQ ID NO: 26);
AGYAVFSSVCSFYLPMAVIVVMYC (SEQ ID NO: 27);
LAIVVGVFVLCWFPFFFVLPLGSL (SEQ ID NO: 28); and
EGVFKVIFWLGYFNSCVNPLIYPCS (SEQ ID NO: 29).

80. (new) The method according to claim 67 wherein the amino acid sequence of the peptide is selected from the group consisting of:

VFKVIFWLGYFNSCVN (SEQ ID NO: 31); and
VFKVIFWLGYFNS (SEQ ID NO: 32).

81. (new) The method according to claim 67 or 68 wherein the mammal is a human.

82. (new) The method according to claim 67 or 68 where in the peptide is administered in combination with a pharmaceutically acceptable carrier.

83. (new) The method according to claim 82 wherein the pharmaceutically acceptable carrier enhances stability of the peptide.

84. (new) The method according to claim 82 wherein the pharmaceutically acceptable carrier enhances adsorption of the peptide.

85. (new) The method according to claim 67 or 68 wherein the peptide is administered by a route selected from the group consisting of oral, nasal, buccal, intravenous, intramuscular, subcutaneous and transdermal.

86. (new) A method of treating hypertension in a human in need of said treatment consisting essentially of administering an effective amount of a peptide comprising at least nine contiguous amino acids residues selected from an amino acid sequence of a transmembrane domain of an alpha-1A adrenergic receptor.

Summary of the Office Action

1. Claims 18, 20 to 37 and 60 to 65 were rejected under 35 U.S.C. 112 (second paragraph) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention.

2. Claims 18, 20 to 26, 28 to 30, 32, 33, 35 to 37 and 60 to 65 were rejected under 35 U.S.C. 112 (first paragraph) for allegedly not being sufficiently enabled by the specification.

3. Claims 18, 20 to 26, 28 to 30, 32, 33, 35 to 37 and 60 to 65 were rejected under 35 U.S.C. 112 (first paragraph) as allegedly failing to comply with the written description requirement.

4. Claims 18, 20 to 22, 36 and 60 to 61 were rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Lofts *et al.* (1993) Oncogene 8, 2813-2820.

5. Claims 18, 20 to 24, 26, 28, 29, 36, 37, 60 and 61 were rejected under 35 U.S.C. 102(e) as allegedly being anticipated by Murphy *et al.* (1996) U.S. Patent 5,508,384.

Response to the Office Action

The Office Action dated August 13, 2003 has been carefully reviewed and the following amendments and comments are made in response. In view of the above amendments and following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims. The amendment to the specification was necessary to correct a typographical error. Applicants respectfully submit that no new prohibited matter has been introduced by the amendments. While written description support for the claims can be found throughout the specification, specific support for these new dependent claims can be found as indicated in the following chart.

Claim	Support
67, 81, 86	Page 29, lines 17 to 21
68	Page 19, lines 4 to 9
69	Page 10, lines 16 to 30
70	Page 27, lines 16 to 24
71	Page 70, lines 1 to 27
72, 73	Page 11, lines 28 to 33
74, 75	Page 17, line 18 to Page 19, line 4
76, 77, 78	Page 21, lines 3 to 6
79	Page 28, line 30 to page 29, line 6

Claim	Support
80	Page 29, lines 12 to 16
82, 83	Page 20, lines 2 to 17
84	Page 20, lines 18 to 26
85	Page 19, lines 31 to 34

Rejection under 35 U.S.C. 112 (second paragraph)

Claims 18, 20 to 37 and 60 to 65 were rejected under 35 U.S.C. 112 (second paragraph) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention.

Applicants have cancelled these claims without prejudice or disclaimer and without acquiescing to the merits of the rejection. Applicants submit that the substitute claims now clearly encompass a method of administering a peptide and not an expression vector based upon the language set forth in claims 67, 68 and 86.

Rejection under 35 U.S.C. 112 (first paragraph)

Claims 18, 20 to 26, 28 to 30, 32, 33, 35 to 37 and 60 to 65 were rejected under 35 U.S.C. 112 (first paragraph) as allegedly not being reasonably enabled by the specification for effective analogues or fragments of peptides or peptides of at least four amino acids of a transmembrane domain of a selected receptor protein. Applicants have cancelled these claims without prejudice or disclaimer and without acquiescing to the merits of the rejection.

Applicants submit that the specification provides sufficient enablement for the substitute claims. Specifically, the substitute claims require administration of peptides containing at least nine contiguous peptides from a transmembrane domain of the alpha-1A adrenergic receptor for the treatment of hypertension. Contrary to the statement in the previous Office Action that the specification only discloses peptides as short as fourteen amino acids (see page 5), Applicants bring to the attention of the Examiner that the specification discloses both *in vitro* and *in vivo* experimental data demonstrating the efficacy of peptides as small as nine amino acid residues (see, for example, page 60, line 3 to page 61, line 10). Furthermore, i*n vivo* experimental data for inhibition of drug-induced increases in blood pressure (*i.e.*, hypertension) associated with alpha-1A adrenergic receptor activity can be found in Example 5 of the specification (see page 70). Finally, the previous Office Action indicated that the specification was enabling for the claimed peptide sequences that are antagonists to D1 or D2 dopamine receptors, or beta-1

or alpha-1A adrenergic receptors (see Office Action dated August 13, 2003 at page 4).

With regard to claim 68 relating to conservative amino acid substitutions in the nine contiguous amino acids selected from a transmembrane domain, the substitute claims now embody a method of treating hypertension with a peptide containing one or more conservative substitutions. The Office Action indicated that the specification provides no guidance as to which amino acid residues in the transmembrane sequence can be changed to yield a functional equivalent. Applicants bring to the attention of the Examiner the examples of conservative amino acid substitutions disclosed in the specification (see page 19, lines 4 to 9). Given this disclosure in the specification, Applicants submit that the skilled artisan could readily determine which conservative substitutions are encompassed in claim 68 to practice the invention without undue experimentation.

Claims 18, 20 to 26, 28 to 30, 32, 33, 35 to 37 and 60 to 65 were also rejected under 35 U.S.C. 112 (first paragraph) as allegedly failing to comply with the written description requirement. Applicants have cancelled these claims without prejudice or disclaimer and without acquiescing to the merits of the rejection.

Applicants submit that the substitute claims meet the written description provision of 35 U.S.C. 112 (first paragraph) because the specification provides multiple examples of peptides derived from the transmembrane domains of the alpha-1A adrenergic receptor that are effective for modulating receptor activity as well as other related G protein-coupled receptors (see, for example, Example 5 on page 70). Furthermore, the Office Action acknowledges that the specification provides sufficient written description for a method of treating a disorder for which administration of a specific antagonist of either the D2 dopamine receptor, beta-1 adrenergic receptor or an alpha-1A adrenergic receptor is effective (see Office Action dated August 13, 2003 at page 9).

With regard to conservative substitutions in the nine contiguous amino acids as set forth in substitute claim 68, Applicants bring to the attention of the Examiner that the specification sets forth that a peptide containing a conservative amino acid substitution must retain activity (see page 13, lines 6 to 12). Furthermore, Applicants submit that the comments relating to the Townsend-Nicholson *et al.* reference set for the previous Office Action are not applicable to the substitute claims because a mutation which alters activity cannot, by definition, be a conservative substitution. The situation where a single amino acid substitution eliminates the activity of a protein is generally an exception to the rule rather than the more common situation where multiple conservative substitutions can be made without affecting protein function.

Rejection under 35 U.S.C. 102(b)

Claims 18, 20 to 22, 36 and 60 to 61 were rejected under 35 U.S.C. 102(b) as being anticipated by Lofts *et al.* Applicants have cancelled these claims without prejudice or disclaimer and without acquiescing to the merits of the rejection. Applicants submit that the cited reference makes no reference to treatment of hypertension nor the alpha-1A adrenergic receptor and therefore does not contain all the limitations of the substitute claims.

Rejection under 35 U.S.C. 102(e)

Claims 18, 20 to 24, 26, 28, 29, 36, 37, 60 and 61 were rejected under 35 U.S.C. 102(e) as being anticipated by Murphy *et al.* Applicants have cancelled these claims without prejudice or disclaimer and without acquiescing to the merits of the rejection. Applicants submit that the cited reference makes no reference to treatment of hypertension in the context of the alpha-1A adrenergic receptor and therefore does not contain all the limitations of the substitute claims. Furthermore, the cited reference makes no distinction among the subtypes of alpha-1A adrenergic receptors. Applicants submit that Murphy *et al.* is not applicable as prior art to the substitute claims in the absence of a disclosure of the alpha-1A adrenergic receptor in the context of the treatment of hypertension.

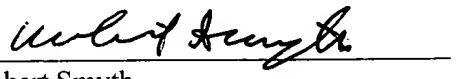
Conclusion

Applicants respectfully request reconsideration of the subject application in view of the substitute claims and the above remarks. It is respectfully submitted that this application is now in condition for allowance. Should the Examiner believe it to be useful, an interview with the Examiner is respectfully requested in order to discuss the foregoing claims.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application, including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or

credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **constructive petition for extension of time** in accordance with 37 C.F.R. 1.136(a)(3).

Respectfully submitted
Morgan, Lewis & Bockius LLP



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Dated: **February 13, 2004**
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